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Erythromycin, QTc interval prolongation, and *torsade de pointes*: Case reports, major risk factors and illness severity

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***Abstract*:**
Objectives: Erythromycin is a macrolide antibiotic that is widely used for various infections of the upper respiratory tract, skin, and soft tissue. Similar to other macrolides (clarithromycin, azithromycin), erythromycin has been linked to QTc interval prolongation and *torsade de pointes* (*TdP*) arrhythmia. We sought to identify factors that link to erythromycin-induced/associated QTc interval prolongation and *TdP*.
Methods and Results: In a critical evaluation of case reports, we found 29 cases: 22 women and 7 men (age range 18–95 years). With both oral and intravenous erythromycin administration, there was no significant relationship between dose and QTc interval duration in these cases. Notably, all patients had severe illness. Other risk factors included female sex, older age, presence of heart disease, concomitant administration of either other QTc prolonging drugs or agents that were substrates for or inhibitors of CYP3A4. Most patients had at least two risk factors.
Conclusions: On the basis of case report evaluation, we believe that major risk factors for erythromycin-associated *TdP* are female sex, heart disease and old age, particularly against a background of severe illness. Coadministration of erythromycin with other drugs that inhibit or are metabolized by CYP3A4 or with QTc prolonging drugs should be avoided in this setting.

***Keywords*:** drug-induced QTc interval prolongation, erythromycin, risk factors, *torsade de pointes*

Introduction

Erythromycin has been used since the 1950s for various infections of the upper respiratory tract, skin, and soft tissue and as a penicillin substitute in patients allergic to penicillin [Zuckerman, 2004]. However, it was not until 30 years later that clinicians recognized its link to QTc interval prolongation and *torsade de pointes* (*TdP*) [McComb *et al.* 1984; Guelon *et al.* 1986; Freedman *et al.* 1987; Ragosta *et al.* 1989].

Oral erythromycin and sudden cardiac death

Ray and colleagues studied the oral administration of erythromycin and its link to sudden cardiac death (SCD) in a Tennessee Medicaid cohort that comprised 1,249,943 person-years of follow up and 1476 cases of confirmed SCD [Ray *et al.* 2004]. CYP3A4 inhibitors employed in this study were nitroimidazole antifungal drugs, diltiazem, verapamil, and troleandomycin. Each inhibitor at least doubled the area under the time–concentration curve for a CYP3A4 substrate. To assess possible confounding by indication, amoxicillin (antibiotic with similar indications as erythromycin that does not prolong QTc interval) and previous use of erythromycin were also studied. SCD among patients currently using oral erythromycin was twice as great compared with patients not using any of the study antibiotics. Former use of erythromycin or current use of amoxicillin did not increase the risk of SCD. Among patients coadministered

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erythromycin and a CYP3A4 inhibitor, there was a fivefold increase in the risk of SCD compared with patients using neither CYP3A4 inhibitors nor study antibiotics. Among patients receiving amoxicillin and CYP3A4 inhibitors or those currently using any of the study medications, there was no increased risk of SCD. Ray and colleagues concluded that the coadministration of erythromycin and strong CYP3A4 inhibitors should be avoided [Ray *et al.* 2004].

Ray and colleagues commented on both oral and intravenous (IV) erythromycin-related QTc interval prolongation and *TdP*, but did not identify the risk factors for either of those electrocardiographic (EKG) parameters in their study [Ray *et al.* 2004]. They noted that IV administration of erythromycin more closely links to drug-induced QTc interval prolongation and *TdP* than oral administration. Women comprised at least two-thirds of the study cohort and between 16.8% and 26.0% of them were elderly. No attempt was made to judge the severity of patients' medical illness.

QTc interval prolongation among critically ill patients receiving IV erythromycin lactobionate slowly

Tschida and colleagues noted that rapid IV infusion of erythromycin had recently (as of 1996) been linked to QTc interval prolongation, *TdP*, and SCD [Tschida *et al.* 1996]. The authors prospectively studied the relationship between QTc interval prolongation and slow (8.9 ± 3.5 mg/minute, range 3.9–16.7 mg/min) IV infusion of erythromycin lactobionate in 44 critically ill patients receiving IV antibiotics (half receiving erythromycin and the other half ceftazidime, cefuroxime, cefotaxime, ceftriaxone, or ampicillin–sulbactam as controls). Cardiac monitor rhythm strips were taken immediately before and within 15 minutes after completing drug infusion. The authors evaluated only the first set of rhythm strips. No patients demonstrated liver dysfunction but two controls did.

The Bazett formula was used to calculate the QTc interval. Tschida and colleagues [Tschida *et al.* 1996] did not discuss the limitations of measuring the QTc interval in drug/illness-induced heart rate changes, particularly in the setting of rapid heart rate, a likely finding in critically ill patients [Indik *et al.* 2006]. For controls, there was no change ($p = 0.712$) in QTc interval at baseline (423 ± 96 ms, range 300–550 ms) and after infusion (419 ± 96 ms, range 280–610 ms). Among erythromycin patients, these differences reached statistical significance ($p = 0.034$; baseline 524 ± 105 ms, range 360–810 ms; and after infusion 555 ± 134 ms, range 400–980 ms). That is, erythromycin patients largely maintained QTc interval measurements above the critical threshold of 500 ms, a value associated with *TdP* [Bednar *et al.* 2001, 2002; Yap and Camm, 2003]. No patients developed *TdP* during erythromycin infusion. However, the authors concluded that slow IV infusion of erythromycin lactobionate was associated with significant QTc interval prolongation.

In a prospective study, Haefeli and colleagues sought to determine the incidence of QTc interval prolongation and ventricular arrhythmia (VA) in a consecutive series of seven critically ill patients treated with IV erythromycin in a medical ICU of a university hospital [Haefeli *et al.* 1992]. Erythromycin was administered over the course of a short infusion and QTc interval was measured before and after antibiotic treatment along with other variables. QTc interval prolongation appeared during 12 of 13 erythromycin infusions in these seven study patients. The magnitude of QTc interval prolongation correlated with erythromycin infusion rate ($r = 0.765$, $p = 0.05$). In three study subjects, VAs occurred in close temporal relationship to antibiotic infusion. Two of these three developed ventricular fibrillation shortly after the first and second doses of erythromycin, respectively, and died within 3 hours. The authors concluded that erythromycin-induced QTc interval prolongation appears frequently and correlates with antibiotic infusion rate. They recommended that the slowest possible infusion rate be used and subjects undergo careful cardiac monitoring.

Less critically ill patients receiving erythromycin lactobionate

In a retrospective study of all inpatients receiving IV erythromycin lactobionate over the course of 1 year in a university teaching hospital setting, Oberg and Bauman [Oberg and Bauman, 1995] sought to determine the frequency of QTc interval prolongation (Bazett) and *TdP* among patients receiving this drug intravenously. A total of 278 patients, all receiving antibiotic treatment for suspected atypical pneumonia (*Legionella pneumophila*, *Mycoplasma pneumoniae*), were available and 49 (26 men and 23 women, ages 22–91, 51 ± 18 years) of them had EKGs while receiving and not receiving

erythromycin (baseline QTc interval 432 ± 39 ms [range 373–532 ms] and 483 ± 62 ms [range 350–670 ms] while receiving erythromycin). A total of 30 (61.2%) of these 49 subjects had heart disease and QTc interval increase was 15 ± 11% compared with 8.6 ± 10% for the patients without heart disease. QTc interval prolongation was not related to erythromycin dose (mg/kg/day); however, among the nine patients receiving 60 mg/kg/day or greater, increase in QTc interval was greater than 15%. A total of 19 (39%) of the 49 study patients developed QTc interval prolongation ≥500 ms during erythromycin infusion and one of the 278 patients receiving erythromycin lactobionate during the study period of 1 year developed *TdP* (0.36%). The authors concluded that (1) erythromycin lactobionate treatment commonly induces QTc interval prolongation but rarely links to *TdP* and (2) heart disease is an important risk factor.

The one patient who developed *TdP* was a 72-year-old woman with both coronary and valvular heart disease, severe liver dysfunction, and hypertension. She is Case #18 in Table 1 and Online Appendix A.

Erythromycin pharmacology

Pharmacokinetics

The oral bioavailability of erythromycin is low; however, different ester and salt formulations offer improved oral absorption ranging from 45 to 80%. Both erythromycin estolate and ethylsuccinate are dependent upon hydrolysis to erythromycin base for absorption.

Erythromycin has a large volume of distribution and is lipophilic with extensive penetration in body tissues and fluids, including cardiac tissue [Tschida *et al.* 1996]. Serum concentrations appear to be lower than tissue concentrations. The time to reach peak serum concentrations after an oral dose ranges from 2 to 4 hours.

Erythromycin is extensively metabolized by the CYP450 enzyme system and is an inhibitor of several isoenzymes. As a result, erythromycin has a potential for increasing serum concentrations of drugs metabolized via this system. The interaction of erythromycin and terfenadine is well documented to cause QTc interval prolongation by both increased serum terfenadine concentrations by CYP450 enzyme inhibition of erythromycin and by erythromycin itself [Paris *et al.* 1994; Biglin *et al.* 1994]. The half-life of erythromycin is 2–3 hours. Biliary excretion is responsible for erythromycin elimination and only minute amounts of drug are cleared renally.

Pharmacodynamics

Macrolide antimicrobials, including erythromycin, display time-dependent antibacterial activity. Antimicrobials that are time-dependent require serum drug concentrations above the minimum inhibitory concentration for an extended time period to allow for antimicrobial activity. Erythromycin also displays antimicrobial activity after drug exposure, often termed the post-antibiotic effect [Zhanel *et al.* 2001].

Erythromycin as a hERG channel inhibitor

Drugs that cause QT interval prolongation and *TdP* tend to share in common an ability to produce pharmacological inhibition of hERG (*human Ether-a-go-go Related Gene*) potassium ion channels [Vandenberg *et al.* 2001; Hancox *et al.* 2008]. hERG is responsible for the rapid delayed rectifier K^+ current, I_{Kr}, in cardiac myocytes, which regulates ventricular action potential (AP) repolarization and, thereby, the QT interval duration.

Macrolide antibiotics are well established to inhibit hERG channel current (I_{hERG}) [Volberg *et al.* 2002; Stanat *et al.* 2003]. Volberg and colleagues reported I_{hERG} inhibition in a mammalian cell expression system by erythromycin with a half maximal inhibitory concentration (IC_{50}) of 72.2 μM, whilst in the same study its metabolite desmethyl-erythromycin also produced weaker I_{hERG} inhibition (IC_{50} of 147.1 μM). Some subsequent studies have reported lower I_{hERG} block IC_{50} values for erythromycin of 38.9 μM [Stanat *et al.* 2003], 59.3 μM [Duncan *et al.* 2006], and 21 μM [Wisialowski *et al.* 2006].

Two studies have reported a marked temperature sensitivity of the inhibitory action of erythromycin against I_{hERG} [Kirsch *et al.* 2004; Guo *et al.* 2005]. One of these studies demonstrated an approximately linear increase in I_{hERG} block by the drug over a temperature range between 36°C and 42°C, whilst also demonstrating markedly temperature-sensitive AP prolongation over a range from 22°C to 42°C [Guo *et al.* 2005]. It is feasible that temperature-sensitivity of I_{hERG} block by erythromycin over a range encompassing physiological temperatures and those relevant

Table 1. Risk factors for QTc interval prolongation and *torsades de pointes* (*TdP*) by case reports among patients receiving erythromycin (ERM).

Case/illness severity/arrhythmia	QTc (ms)	ERM daily dose/PO/IV	Female sex	Elderly	Heart disease	Hepatic/renal failure	Hypo-K^+	Hypo-Mg^{++}	Bradycardia	CYP3A4 substrate/ inhibitor	QTc-prolonging drugs	Naranjo Scale	WHO-UMC	Additional risk factors
#1 McComb *et al.*, 1984 / 3+ / Ventricular Tachycardia	603 ms	1000 mg IV	Yes	Yes	Yes	None reported	No	No	–	None	None	Probable	Probable/ Likely	Acute medical illness, chronic medical illness
#2 Guelon *et al.*, 1986 / 4+ / *TdP*	'Prolonged'	3000 mg IV	Yes	No	Yes	None reported	No	–	–	None	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#3 Freedman *et al.*, 1987 / 3+ / *TdP*, Ventricular Flutter	605 ms	2000 mg PO	Yes	No	Yes	None reported	No	No	No	None	None	Probable	Probable/ likely	Acute medical illness
#4 Ragosta *et al.*, 1989 / 3+ / *TdP*	600 ms	4000 mg IV	Yes	Yes	Yes	None reported	No	–	–	Disopyramide (substrate)	Disopyramide	Possible	Possible	Acute medical illness
#5 Ragosta *et al.*, 1989 / 3+ / *TdP*	630 ms	2000 mg PO	No	Yes	Yes	Acute kidney injury	No	No	–	Disopyramide (substrate)	Disopyramide	Possible	Possible	Acute medical illness, chronic medical illness
#6 Schoenenberger *et al.*, 1990 / 3+ / *TdP*	550 ms	3000 mg IV	Yes	No	Yes	Potential hepatic disease – elevated LFTs	No	No	–	None	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#7 Lindsay, Jr. *et al.*, 1990 / 3+ / *TdP*	640 ms	Unknown IV	No	No	No	None reported	No	No	–	None	Pentamidine	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#8 Lindsay, Jr. et al., 1990 / 3+ / *TdP*	'Prolonged'	Unknown IV	Yes	No	No	Cadaveric kidney transplant with rejection	No	No	No	None	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#9 Nattel *et al.*, 1990 / 4+ / *TdP*	600 ms	4000 mg IV	No	Yes	Yes	Renal dysfunction – elevated Cr and BUN	No	No	–	Amiodarone (inhibitor) quinidine (substrate)	Amiodarone, quinidine (stopped 2 days before ERM)	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#10 Haefeli *et al.*, 1992 / 4+ / *TdP*	562 ms	1000 mg IV	No	No	No	Renal dysfunction (kidney graft)	–	–	–	None	None	Possible	Possible	Acute medical illness, chronic medical illness
#11 Haefeli *et al.*, 1992 / 4+ / Ventricular tachycardia	500 ms	1000 mg IV	No	Yes	No	None reported	No	No	–	None	None	Possible	Possible	Acute medical illness, chronic medical illness
#12 Paris *et al.*, 1994 / 3+ / *TdP*	531 ms	2000 mg PO	Yes	No	No	None reported	No	No	Yes	Terfenadine (substrate)	Terfenadine	Possible	Possible	Acute medical illness, chronic medical illness
#13 Brandriss *et al.*, 1994 / 4+ / *TdP*	600 ms	4000 mg IV	Yes	No	Yes	None reported	No	No	–	None	None	Probable	Probable/ Likely	Acute medical illness, chronic medical illness
#14 Gitler *et al.*, 1994 / 4+ / *TdP*	670 ms	3000 mg IV	Yes	Yes	Yes	None reported	No	–	–	None	None	Possible	Possible	Acute medical illness, chronic medical illness
#15 Gitler *et al.*, 1994 / 4+ / *TdP*	660 ms	1000 mg IV	Yes	Yes	Yes	None reported	No	No	No	None	None	Probable	Possible	Acute medical illness,chronic medical illness

(continued)

Table 1. Continued.

Case/illness severity/arrhythmia	QTc (ms)	ERM daily dose/PO/IV	Female sex	Elderly	Heart disease	Hepatic/renal failure	Hypo-K^+	Hypo-Mg^{++}	Bradycardia	CYP3A4 substrate/ inhibitor	QTc-prolonging drugs	Naranjo Scale	WHO-UMC	Additional risk factors
#16 Rezkalla & Pochop, 1994 / 4+ / *TdP*	517 ms	Unknown IV	Yes	Yes	Yes	None reported	No	No	–	None	None	Probable	Probable/ Likely	Acute medical illness, chronic medical illness
#17 Biglin *et al.*, 1994 / 4+ / *TdP*, Ventricular fibrillation	630 ms	1000 mg PO	Yes	No	No	None reported	No	No	–	Terfenadine (substrate)	Terfenadine	Possible	Possible	Acute medical illness
#18 Oberg & Bauman, 1995 / 3+ / *TdP*	560 ms	4000 mg IV	Yes	Yes	Yes	Severe liver disease.	No	No	–	None	None	Probable	Probable	Acute medical illness, chronic medical illness
#19 Wong & Windle, 1995 / 4+ / *TdP*	550 ms	1000 mg IV	Yes	No	No	None reported	Yes	–	–	Fluconazole (inhibitor)	Fluconazole	Possible	Possible	Acute medical illness, chronic medical illness
#20 Orban *et al.*, 1995 / 4+ / *TdP*, Ventricular fibrillation	680 ms	4000 mg IV	Yes	No	Yes	Renal transplant with chronic rejection	Yes	No	Yes	Cimetidine (inhibitor)	None	Probable	Probable/ Likely	Acute medical illness,chronic medical illness
#21 Chennareddy et al., 1996 / 3+ / Polymorphic ventricular tachycardia	320 ms	1000 mg IV	No	No	No	None reported	No	No	No	None	None	Possible	Probable/ Likely	Acute medical illness,chronic medical illness
#22 Hsieh *et al.*, 1996 / 3+ / *TdP*	700 ms	1000 mg PO	Yes	No	Yes	None reported	No	No	–	None	Astemizole	Possible	Possible	Acute medical illness
#23 Katapadi *et al.*, 1997 / 3+ / *TdP*	720 ms	4000 mg IV	Yes	No	Yes	None reported	–	–	No	None	None	Probable	Probable/ likely	Acute medical illness
#24 Lin & Quasny, 1997 / 3+ / *TdP*	631 ms	1500 mg PO	No	Yes	Yes	None reported (slightly elevated Cr and BUN)	No	No	No	Quinidine (substrate)	Quinidine	Possible	Possible	Acute medical illness, chronic medical illness
#25 Vogt & Zollo, 1997 / 3+ / QT prolongation, narrow-complex tachycardia	640 ms	4000 mg PO	Yes	Yes	No	Renal insufficiency	–	–	Yes	None	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#26 Koh, 2001 / 3+ / *TdP*	612 ms	1000 mg PO	Yes	Yes	Yes	None reported	Yes	No	Yes	Carbimazole (minor inhibitor)	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#27 Goldschmidt *et al.*, 2001 / 3+ / QT prolongation	583 ms	2000 mg PO	Yes	Yes	Yes	None reported	No	No	Yes	Verapamil (inhibitor)	None	Probable	Probable/ likely	Acute medical illness, chronic medical illness
#28 Kyrmizakis *et al.*, 2002 / 3+ / *TdP*, Ventricular fibrillation	'Prolonged'	2000 mg PO	Yes	No	No	None reported	No	No	No	Cisapride (substrate)	Cisapride	Possible	Possible	Acute medical illness, chronic medical illness
#29 Hinterseer *et al.*, 2006 / 4+ / *TdP*, Ventricular fibrillation	510 ms	4000 mg IV	Yes	No	Yes	None reported	No	Yes	–	None	None	Possible	Possible	Acute medical illness

to pyrexia may have functional significance [Guo *et al.* 2005]. Erythromycin has also been reported to have synergic effects with β-estradiol on I_{hERG} [Ando *et al.* 2011].

In monophasic AP recordings from anesthetized guinea-pigs, erythromycin has been observed to increase both AP duration and alternans [Wisialowski *et al.* 2006]. The drug has also been shown to increase AP duration in a concentration dependent fashion in rabbit Purkinje fibers and to prolong both QT interval and T_{peak}–T_{end} in a concentration-dependent fashion in an arterial perfused rabbit left ventricular wedge preparation [Lu *et al.* 2007]. At the highest concentration tested (300 μM), the drug elicited early-after-depolarizations (EADs) in 6 of 7 wedge preparations tested [Lu *et al.* 2007].

Methods

We conducted a critical evaluation (until and including 1 August 2013) of case reports. Initially, we entered the following MeSH terms: 'erythromycin and qtc prolongation' and 'erythromycin and torsade' into Medline. We searched CredibleMeds (http://www.azcert.org/) for case report of erythromycin, QTc interval prolongation, and *TdP* This search was initiated via AZCERT: ("Erythromycin"[MeSH] AND ("Long QT Syndrome"[MeSH] OR "Torsades de Pointes"[MeSH])) OR (((torsade[ti] OR torsadegenic[ti] OR torsades[ti] OR torsadogenesis[ti] OR torsadogenic[ti] OR torsadogenicity[ti]) OR qt[ti]) AND erythromycin[ti]). We searched EMBASE and Cochrane only for case reports. Only human studies were included. We also reviewed reports from our files and reference lists. This process yielded a total of 29 cases as shown in Table 1. (A more detailed case narrative appears in Online Appendix A.) Titles and abstracts were independently reviewed by two investigators (WVRV and AB). Disagreement was resolved by consensus. Assessment of causality was estimated using the 'Naranjo' scale for estimating probability of adverse drug reactions [Naranjo *et al.* 1981] and also the 'WHO-UMC' system for standardized case causality assessment (see http://who-umc.org/Graphics/24734.pdf).

Results

We found 29 cases (22 women and 7 men; see Table 1) all of which involved adults (age range 18–95 years; mean 57.5 years [±3.9 standard error of the mean (SEM)], median 59 years, 22 of 29 cases were in individuals older than 40). The reports ranged from 1984 to 2006, with no reports subsequent to 2006 matching our search criteria. Among the 24 cases with both reported erythromycin dose and concurrent QTc interval measurement, we found no statistically significant relationship between erythromycin dose and QTc interval duration in either parametric or non-parametric analyses (Pearson $r = 0.219$, $p = 0.305$; Spearman $r = 0.108$, $p = 0.614$). These findings did not change when cases were separated into groups according to intravenous and oral administration routes. A total of 15 cases involved IV administration (Pearson $r = 0.401$, $p = 0.138$; Spearman $r = 0.324$, $p = 0.239$), whilst nine involved oral administration (Pearson $r = -0.148$, $p = 0.704$; Spearman $r = -0.236$, $p = 0.552$). Major risk factors were female sex (22 cases), heart disease (19 cases) and elderly (13 cases). In 11 cases, patients received other drugs that were either substrates for or inhibitors of CYP3A4, whilst concomitant administration of other QT interval prolonging drug was present in 10 cases. Only seven cases contained evidence of clear renal or hepatic disease/dysfunction. Hypokalemia was found in three cases and hypomagnesemia in 1. Unsurprisingly, given the clinical indications for erythromycin use, all patients had an acute medical illness, whilst 23 of the 29 cases also had a chronic illness (further details are available in the detailed narrative of the case reports in Online Appendix A). We categorized overall severity of illness according to patient management: 1+ representing management as an outpatient; 2+ requiring hospitalization; 3+ requiring admission to ICU and/or careful cardiac monitoring; 4+ requiring some aspect of life support other than cardioversion. A total of 17 cases exhibited illness severity 3+ and the remaining 12 exhibited illness severity 4+. Of the cases for which both QT interval and dose information are available, all possessed at least one risk factor additional to erythromycin treatment and many cases possessed multiple risk factors. One case (#21), reporting polymorphic VT with a QTc interval at the lower end of the normal range (320 ms), exhibited none of the additional tabulated risk factors except for the presence of both acute and chronic illness. Causality assessment according to the Naranjo scale and WHO-UMC criteria led to assessments ranging from possible to probable on the Naranjo scale and from possible to probable/likely on the WHO-UMC scale (see Table 1). It should be noted in respect of causality assessment that: (i) information for Naranjo

scale questions 6–9 was seldom present, limiting appropriate application of the scale criteria; (ii) identifying alternate causes, which can lessen the overall score, is open to subjective opinion; and (iii) assessment of 'certainty' of adverse effect can benefit from a formal challenge–dechallenge–rechallenge protocol, which may not be possible or desirable to apply systematically in a setting where a potentially life-threatening arrhythmia has occurred. It is notable, however, that appearance of QTc prolongation/*TdP* was identifiably coincident with intravenous erythromycin administration in some cases (see narratives for cases #6 and #9 in Online Appendix A).

Discussion

Erythromycin and surrogate markers of TdP

Drug-induced *TdP* is a comparatively rare, albeit serious, side effect and consequently proxy (surrogate) markers are used to evaluate *TdP* risk. hERG block is a key preclinical surrogate, though an insufficient predictor of arrhythmia on its own [Hancox *et al.* 2008; Gintant, 2008]. QTc prolongation is also clearly a marker of arrhythmia rather than arrhythmia *per se*. The delayed repolarization resulting from pharmacological hERG/I_{Kr} inhibition is commonly considered to be linked to *TdP* through cellular EADs (as an arrhythmia trigger) and exacerbation of transmural dispersion of repolarization (as a substrate for re-entrant arrhythmia). For more in-depth consideration of drug-induced *TdP* mechanisms the reader is referred to Yap and Camm [Yap and Camm, 2003], Hancox and colleagues [Hancox *et al.* 2008], and Gintant [Gintant, 2008].

Drug-induced *TdP* is difficult to predict on an individual basis, but QTc prolongation is most commonly associated with arrhythmia at QTc intervals of >500 ms or more [Bednar *et al.* 2001; Yap and Camm, 2003]. Of the 29 cases examined here (Table 1), QTc interval data are available for 26: of these, only one case had a QTc interval of <500 ms and 16 cases had QTc intervals of 600 ms or greater. This is in broad agreement with an earlier review of eight cases of *TdP* with erythromycin found patients had QTc intervals between ~560 ms and 700 ms [Gitler *et al.* 1994]. The lack of a clear correlation between erythromycin dose and QTc interval in our analysis is suggestive that, in the setting of patients experiencing erythromycin-induced arrhythmia, drug dose alone is not strongly predictive of outcome.

Erythromycin-induced TdP *as a 'multiple hit' phenomenon*

As drug-induced *TdP* is an infrequent occurrence, it is most likely to occur when multiple 'hits' coincide to precipitate arrhythmia induction [Keating and Sanguinetti, 2001]. In the setting of administration of a hERG/I_{Kr} blocking drug, the other 'hits' either exacerbate the I_{Kr}/hERG-blocking effects of the drug or otherwise diminish ventricular repolarization reserve [Kannankeril and Roden, 2007]. Yap and Camm [Yap and Camm, 2003] have noted the following factors that are likely to increase prolongation of ventricular repolarization or *TdP* liability: organic heart disease; metabolic (including electrolyte) abnormalities; hepatic impairment; drug related factors (including narrow therapeutic index and effects on cytochrome P450); female sex. In a study of 249 patients who experienced *TdP* with noncardiac drugs, Zeltser and colleagues identified a number of risk factors of which female sex was the strongest (71% of patients) [Zeltser *et al.* 2003]. Heart disease was seen in 41% of patients and was particularly prevalent in those with *TdP* from antibiotics. A total of 39% of patients received coadministration of two or more drugs associated with QTc prolongation. A total of ~18% of patients had a familial history of long QT syndrome, of prior *TdP*, or a prolonged QT segment of the ECG in the absence of drugs. Electrolyte abnormalities were also present in a proportion of cases. More than 70% of patients had two or more concurrent risk factors [Zeltser *et al.* 2003]. In 2002, Shaffer and colleagues examined risk factors in reports of *TdP* associated with macrolide use, from the FDA's adverse event reporting system (AERS) [Shaffer *et al.* 2002]. A total of 53% of the 156 reports examined involved erythromycin (with 36% and 11% involving clarithromycin and azithromycin). Two-thirds of macrolide-only cases involved women and 37% of macrolide only reports involved concomitant cardiac disease [Shaffer *et al.* 2002]. A 2004 analysis of 25 reports of *TdP* with erythromycin also highlighted female sex (68% of cases) and presence of underlying cardiovascular disease (16 of 21 reports for which information was available) [Owens, 2004]. A subsequent study of reports of *TdP* in 78 patients with antibiotics found 66.7% of all patients to be women, also identifying advanced heart disease and concomitant use of other QT-prolonging agents or inhibitors of

hepatic drug metabolism to be frequently present [Justo and Zeltser, 2006].

The present case report analysis is in good qualitative agreement with these prior analyses, particularly in respect of prevalence of female sex, which in our analysis accounted for ~76% (22/29) of cases. Female preponderance of drug-induced *TdP* is likely linked to well-established sex differences in ventricular repolarization and in the underlying ionic currents [Abi-Gerges *et al.* 2004; James *et al.* 2007]. Our analysis in respect of concurrent heart disease (19/29, ~66%) is also in agreement with, though gives a greater incidence of presence of heart disease than, those reported in some previous analyses [Zeltser *et al.* 2003; Shaffer *et al.* 2002], though not others [Owens, 2004]. Impaired hepatic function or concomitant receipt of other drugs that are substrates for or inhibitors of CYP3A4 (~38% of cases) are significant in that impaired metabolism is likely to lead to increased erythromycin levels, whilst coadministration with other QT prolonging drugs is likely to lead to synergistic effects on hERG/I_{Kr} [Hancox *et al.* 2008]. Class Ia hERG-blocking antiarrhythmic drugs (quinidine/disopyramide) were present in four cases, whilst terfenadine and cisapride, both of which have strongly been associated with hERG block and *TdP*, were present in three. Pentamidine was present in one case and, whilst this drug does not produce acute I_{Kr}/hERG inhibition it impairs hERG trafficking and, thereby, the number of functional I_{Kr} channels in the cell membrane [Kuryshev *et al.* 2005]. One of the longest QTc intervals (case #22; 700 ms) involved coadministration with astemizole, which is one of the most potent hERG blocking drugs thus far identified ($IC_{50} \sim 1$ nM) [Zhou *et al.* 1999]. Whilst impaired renal function was identified in several cases (Table 1), as renal clearance of erythromycin is small it is unclear whether or not impaired renal function would greatly exacerbate risk.

A role for illness severity?

A striking feature of the cases examined here is that all patients had serious illness (illness severity 3+ or 4+; Table 1 and Online Appendix A). This raises a question as to whether or not illness severity may be a factor in the development of erythromycin-linked acquired long QT syndrome? The recent 'QT in Practice' (QTIP) study examined the incidence of QTc interval prolongation in the critical care setting and found episodes of QTc prolongation to >500 ms of 15 minutes or more in 252 of 1039 patients studied (24%) [Pickham *et al.* 2012]. More women than men developed QT prolongation and significant predictors were female sex, administration of QT-prolonging drugs, cerebrovascular incident, hypertension, thyroid disease, diabetes, renal disease, hepatic disease, electrolyte and creatinine abnormalities. Patients with QT prolongation were 'overrepresented in hospital deaths' which was 'attributable to greater illness severity and existing comorbidities' [Pickham *et al.* 2012]. An independent study has recently considered factors influencing mortality in patients in an ICU setting receiving antibiotic therapy for severe bacterial infection [Suefke *et al.* 2012]. When illness severity and antibiotic effect was comparable, survival of women was significantly linked to use of QTc-prolonging drugs, age, and lower body weight. Women with at least two of these factors fared less well than men. The results raise for consideration the issue as to whether or not in such settings QTc-prolonging antibiotics should be replaced in elderly women of low (lean) bodyweight [Suefke *et al.* 2012]. Whilst these recent studies do not prove a causal link between illness severity and QTc prolongation/*TdP*, they are suggestive of an association between illness severity and a poorer outcome, which in the setting of erythromycin therapy may exacerbate the drug's QT-prolonging effect. The mechanism(s) underlying such an association remain to be established, although it is tempting to speculate that increased hERG-block and AP prolongation by erythromycin reported at pyrexic temperatures [Guo *et al.* 2005] could be one contributing factor.

Limitations and strengths of approach

Multiple regression analysis is frequently used to evaluate the effects of more than one independent variable on a dependent variable. However, the assumption is that neither the independent variables nor the dependent variable undergo change in the course of analysis. In the ICU, independent and dependent characterization may change from moment to moment. We believe that risk factors associated with drug-induced QTc interval prolongation and *TdP* may change dynamically and interact in a nonlinear fashion [Vieweg *et al.* 2012, 2013a, 2013b; Kogut *et al.* 2013; Hancox *et al.* 2013]. We therefore suspect that nonlinear dynamics may best describe the interaction of drug-linked QTc

interval prolongation and attendant risk factors to produce *TdP*. At present, we do not have a mathematical approximation of this linkage and must struggle with the clinical setting and risk factors identified from case reports to best understand the potentially fatal cardiac arrhythmia *TdP* [Vieweg *et al.* 2012, 2013a, 2013b; Kogut *et al.* 2013; Hancox *et al.* 2013]. The use of case reports is, however, subject to some limitations. First, plasma drug concentrations at time of *TdP* are not universally available making attractive an analysis based on administered drug dose. Nonetheless, it must be acknowledged that overall drug dose is not necessarily equivalent to subsequent plasma concentration. In this regard, a recent review of antibiotic-induced arrhythmias has highlighted that oral administration of recommended doses of erythromycin is unlikely to lead to drug levels sufficient to produce significant I_{Kr}/hERG blockade, but that rapid IV administration can produce high plasma levels [Abo-Salem *et al.* 2014] which, by extension, would be anticipated to produce a greater effect on I_{Kr}/hERG and thereby repolarization and QTc interval [Abo-Salem *et al.* 2014]. Second, due to the fact that fatalities are not always reported, the evaluation of case reports may be subject to the selection bias inherent in publication of case reports. Third, case reporting can be inconsistent between studies and so, as highlighted recently [Selvaraj *et al.* 2013], the utility of case reports for identifying adverse events would be improved through the use of standardized checklists for reporting, which would include a variety of information incorporating consideration of dechallenge/rechallenge (or their absence) and laboratory results including serum drug levels (for further discussion see Selvaraj and colleagues [Selvaraj *et al.* 2013]). Fourth, because drug-induced *TdP* is a relatively rare event the number of case reports for given drugs is limited and so the results of case study analysis must only be extrapolated to populations with caution. Thus, large group as well as case studies are required in order to gain an overall picture of QTc prolongation with particular drugs. Whilst large cohort analysis and 'thorough QT' studies on healthy volunteers can yield useful information on frequency and extent of QTc prolongation with particular drugs, they are insufficient on their own as they necessarily focus on an arrhythmia surrogate rather than *TdP* itself. In this regard, case studies provide important information.

Comparison with clarithromycin and azithromycin

Whilst the present study is limited to the evaluation of 29 case reports with erythromycin, there is good concordance between its findings and the results of recent analyses of case reports with other macrolide agents (azithromycin and clarithromycin) that we have conducted [Hancox *et al.* 2013; Vieweg *et al.* 2013a; Gysel *et al.* 2013]. For both azithromycin and clarithromycin there was no significant correlation between administered drug dose and QTc interval of the cases examined, whilst female sex, old age and heart disease were identified as major risk factors [Hancox *et al.* 2013; Vieweg *et al.* 2013a]. The present evaluation of erythromycin complements well these recent studies, whilst further identifying illness severity as a factor in the case of erythromycin. A question arises as to whether any of these drugs may be associated with a lower risk than the others of arrhythmia. The limited number of available case reports that we have evaluated (29 in the present study, 12 for azithromycin [Hancox *et al.* 2013], and 21 for clarithromycin [Vieweg *et al.* 2013]) and broad similarity in identified risk factors for the different drugs make us reluctant to speculate in this regard. Azithromycin has received a great deal of interest recently, however, following a high-profile study that showed a small but significantly increased risk of cardiovascular deaths during 5 days of azithromycin therapy [Ray *et al.* 2012]. A recent data-mining study of the FDA AERS over the 8-year period from 2004 to 2011 [Raschi *et al.* 2013] has reported more cases of *TdP* and QT interval abnormalities with azithromycin than for either clarithromycin or erythromycin. When VA and SCD were also taken into account, clarithromycin had a higher number of reports than azithromycin, with erythromycin having fewer reports than either other drug during this period [Raschi *et al.* 2013]. Moreover, whilst erythromycin showed disproportionality with respect to *TdP*/QT abnormalities, azithromycin and clarithryomycin showed disproportionality both with respect to *TdP*/QT abnormalities and for VA/SCD [Raschi *et al.* 2013]. Notably, in this AERS analysis many cases of *TdP*/QT abnormalities with azithromycin occurred in middle-aged rather than elderly individuals, supporting the notion that azithromycin is not necessarily a safer macrolide option in generally healthy patients [Raschi *et al.* 2013]. On the other hand, a separate analysis of a national Danish cohort of 18–64 years of age failed to find an

increased risk of death from cardiovascular causes with azithromycin use [Svanström *et al.* 2013]. In considering the risk with azithromycin, Giudicessi and Ackerman [Giudicessi and Ackerman, 2013] have noted that the exposure (prescription) rates differ between drugs with that for azithromycin being higher; they also noted limitations with the AERS that complicate reliable comparison between the different macrolides. They concluded with respect to azithromycin-related risk for cardiovascular events that 'for most otherwise-healthy patients the absolute risk is miniscule' [Giudicessi and Ackerman, 2013]. Moreover, in a recent independent analysis of azithromycin, Howard has concluded that in the absence of complications or additional risk factors (including female sex, old age, existing cardiovascular disease, and other known risk factors for QTc prolongation), azithromycin is relatively safe, although suggesting that in cases of serious infection in a hospital setting, a baseline ECG should be obtained and electrolytes kept within the normal range [Howard, 2013].

Conclusion

Erythromycin is an effective and widely used antibiotic and QT interval prolongation and cardiac arrhythmia is a rare side effect. Our analysis of the available case report literature suggests that cases of marked QTc prolongation and *TdP* in adults receiving the drug occur predominantly, although not exclusively, in middle-aged and older adults. Major identified risk factors are female sex, old age, and presence of heart disease. Other risks include concomitant administration of drugs that impair erythromycin metabolism or that are associated with QTc prolongation in their own right. Coadministration of erythromycin with such agents should be avoided. In all cases examined here, patients were severely ill. It is therefore reasonable to suggest that erythromycin should be administered with great caution to severely ill patients with concomitant risk factors for QTc prolongation, particularly elderly females and those with heart disease. For severely ill patients in a hospital setting, it would certainly be advisable to take a baseline ECG prior to considering administration of erythromycin, to correct any modifiable risk factors such as electrolyte abnormalities and to repeat ECG monitoring during erythromycin administration, should it be given. The administration of alternative antibiotics free of QTc prolonging effects may be worth considering for severely ill individuals.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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